2. HMGP Synopsis

Clinical Study Report Synopsis: Study F1J-MC-HMGP

Title of Study: Duloxetine 60 mg Once Daily Versus Placebo in the Treatment of Patients with Osteoarthritis Knee Pain	
Number of Investigators: This multicenter study included 39 principal investigators.	
Study Centers: This study was conducted at 39 study centers in 7 countries.	
Publications Based on the Study: None at this time.	
Length of Study: Date first patient enrolled: 16 July 2009 Date last patient completed entire study: 09 February 2010	**Phase of Development:** 3b

Objectives:

The primary objective was to assess the efficacy of duloxetine 60 mg QD compared with placebo on the reduction of pain severity as measured by the Brief Pain Inventory (BPI) – Modified Short Form 24-hour average pain rating (referred to as the BPI average pain rating hereafter) in patients with OA knee pain during a 13-week, double-blind treatment period.

Secondary Objectives:

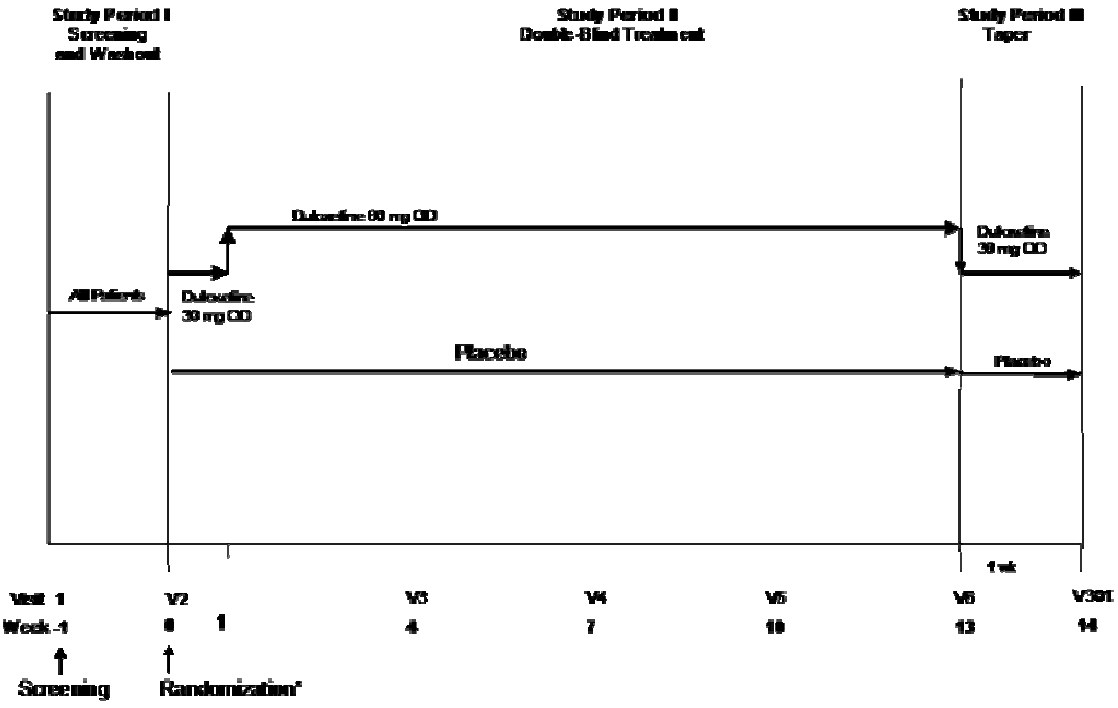
Safety of duloxetine 60 mg QD versus placebo was assessed by way of a comparison of discontinuation rates, adverse events, treatment-emergent adverse events (TEAEs), discontinuations due to adverse events (AEs), serious adverse events (SAEs), changes in laboratory test values, changes in vital signs and weight, and the Columbia Suicide Severity Rating Scale (C-SSRS).

Other secondary objectives were identified and corresponding analyses were planned; however, due to the drug labeling error described in the subsequent section, this report presents results specific to the primary objective and safety-related secondary objectives.

Study Design:
This was a multicenter, randomized, double-blind, parallel, placebo-controlled, Phase 3b study with 3 study periods (approximately 1-week screening period, a 13-week double-blind, acute-therapy treatment period, and a 1-week taper period) conducted in outpatients to assess the efficacy of duloxetine 60 mg QD compared with placebo in the reduction of OA knee pain (see Figure HMGP.2.1). Patients randomly assigned to duloxetine were to start on duloxetine 30 mg QD for 1 week and then, per protocol, were to titrate up to duloxetine 60 mg QD for weeks 2 through 13. Patients randomized to placebo were to receive placebo for weeks 1 to 13.

Following the database lock for this study, and upon preliminary review of efficacy and safety results, a study drug labeling error was suspected. After a thorough investigation of all potential causes that could explain the discrepant results, it was determined that study drug had been mislabeled. The labels for the blinded duloxetine 60 mg bottles and matched placebo-capsule bottles were reversed in the labeling process. The affected study drug materials were those used during weeks 2 through 13 of the acute therapy phase (Study Period II). This resulted in an error in study drug administration, and an uniform violation of the protocol-defined treatment groups for all randomized patients. Table HMGP.2.1 shows the planned, per protocol, treatment regimens and the actual treatment regimens. Figure HMGP.2.2 shows a modified study design that illustrates the actual treatments received as a result of the mislabeled study drug.

Note that per protocol, the study was designed to include a taper period during the last week of the study (Study Period III, Week 14). In this study, due to the crossover of treatment caused by the study drug labeling error, the dose-taper period essentially did not occur. Patients who received duloxetine 60 mg QD for weeks 2 through 13 (pla-duloxetine) did not receive the planned duloxetine 30 mg taper dose, but were instead abruptly discontinued from active treatment and received placebo for Week 14 (Study Period III). Conversely, the patients who had received placebo for weeks 2 through 13 (dlx-placebo) were switched to duloxetine 30 mg QD for Week 14.



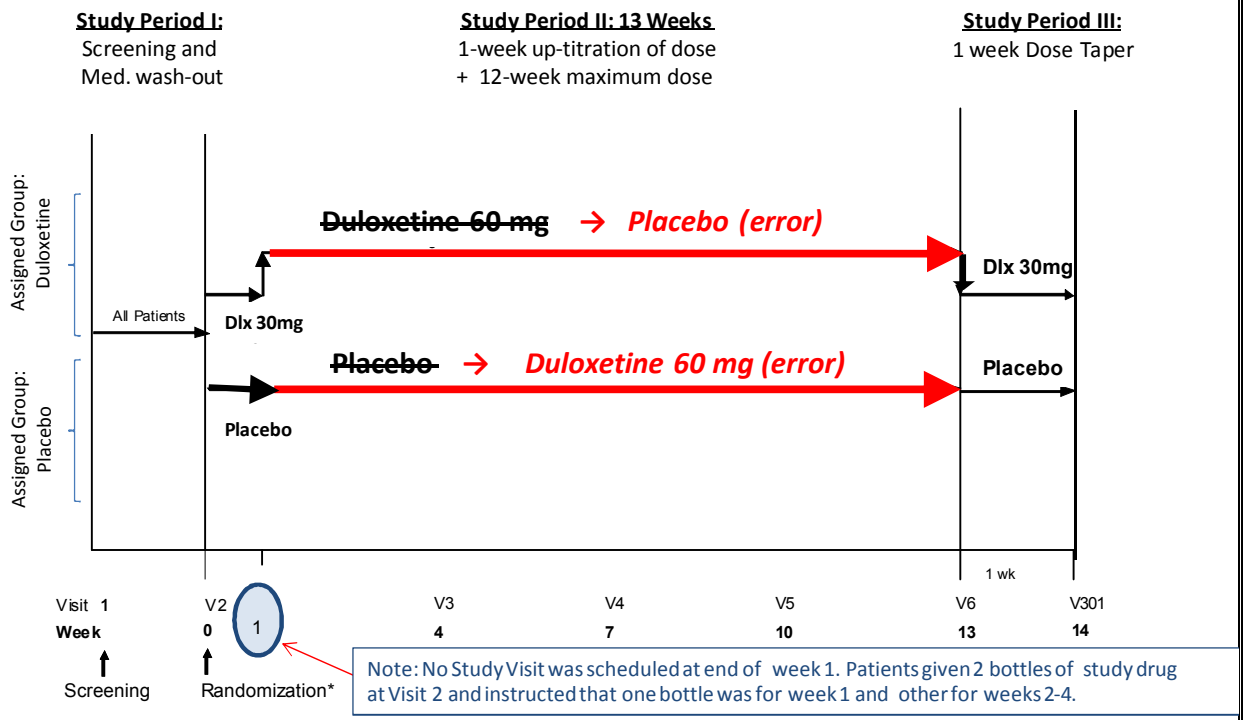
Abbreviations: QD = once daily; V = visits.

Figure HMGP.2.1. Study design: Planned per protocol.

Table HMGP.2.1. Treatment Regimens: Planned and Actual

Study Period	Assigned Treatment	Planned QD Dosage: Duration, Strength, and Form	Actual QD Dosage: Duration, Strength, and Form
I. Screening	None	N/A	N/A
II. Double-Blind Acute Therapy (13 weeks)	DLX	Week 1: 30 mg DLX capsules Weeks 2-13: 60 mg DLX capsules	Week 1: 30 mg DLX capsules Weeks 2-13: **Placebo capsules (ERROR)**
	Placebo	Week 1: Placebo capsules Weeks 2-13: Placebo capsules	Week 1: Placebo capsules Weeks 2-13: **60 mg DLX capsules (ERROR)**
III. Double-Blind Taper (1 week)	DLX	Last Week: 30 mg DLX capsules	Last Week: 30 mg DLX capsules
	Placebo	Last Week: Placebo capsules	Last Week: Placebo capsules

Abbreviations: DLX = duloxetine; N/A = not applicable; QD = once daily; x = times.



Abbreviations: Dlx = duloxetine; Med = medication; Tx = treatment; V = visit; wk = week.

Note: Red text depicts actual study drug administered as a result of drug labeling error.

Figure HMGP.2.2. Study Design: Modified to indicate actual treatments administered.

Number of Patients:
Planned: 650 patients
Randomized: 424 patients (217 pla-duloxetine, 207 dlx-placebo)
Treated (at least 1 dose): 416 patients (213 pla-duloxetine, 203 dlx-placebo)
Completed: 333 patients completed the acute therapy phase/Study Period II (162 pla-duloxetine, 171 dlx-placebo); 332 patients completed Study Period III (162 pla-duloxetine, 170 dlx-placebo). Note that patients could have entered Study Period III if they completed Study Period II, or if they took study drug for at least 2 weeks before discontinuing during Study Period II.

Diagnosis and Main Criteria for Inclusion: Male or female outpatients were eligible to be included in the study if they were at least 40 years of age and met the American College of Rheumatology (ACR) clinical and radiographic criteria for the diagnosis of OA of the knee with pain for greater than or equal to 14 days of each month for 3 months prior to study entry, as well as a pain rating of greater than or equal to 4 on the BPI average pain rating scale at both Visit 1 and Visit 2. The ACR clinical and radiographic criteria for classification of idiopathic OA of the knee include the following criteria: knee pain, osteophytes (with radiographic evidence), and at least 1 of the following: age >50, morning stiffness <30 minutes, or crepitus. Presence of osteophytes in the index knee required documented radiographic evidence from a past imaging study (plain x-ray, computerized tomography, or magnetic resonance imaging), or from a current x-ray taken during the Screening Period.

Study Drug, Dose, and Mode of Administration:
Duloxetine 30 mg (titration and taper purposes only) and 60 mg given orally QD as one 30 mg or 60 mg capsule. Table HMGP.2.1 above summarizes the actual and planned treatment regimens with the actual treatment regimens as the result of the drug labeling error.

Reference Therapy, Dose, and Mode of Administration: Placebo given orally QD as 1 capsule.

Planned Duration of Treatment: 13-week acute therapy phase (including 1 week of titration) followed by a 1-week taper period.
The actual duration of treatment did include a 13-week acute therapy phase (Study Period II) followed by a 1-week Study Period III; however, dosing during each study period is described in Table HMGP.2.1 and Figure HMGP.2.2, above. Following confirmation of the study drug labeling error, the database for the study was unlocked to modify the naming convention used to label the 2 treatment groups. The study database was then relocked. The modified treatment group names were selected to better represent the actual treatments administered, as indicated in Table HMGP.2.2.

Table HMGP.2.2. Treatment Group Naming Convention for Presentation of Statistical Results for Study Period II

Original Assigned Treatment Group	Actual Study Drug Received in 13-week Acute Therapy Phase	Naming Convention Created to Reflect Cross-Over Nature of Each Treatment Group
Duloxetine	Week 1: 30 mg DLX capsules Weeks 2-13: Placebo capsules	Text: dlx-placebo Tables: DLX30QD_PLA
Placebo	Week 1: Placebo capsules Weeks 2-13: 60 mg DLX capsules	Text: pla-duloxetine Tables: PLA_DLX60QD

Abbreviations: DLX = duloxetine; pla = placebo; QD = once daily.

Variables:

Efficacy:

Change from baseline in the BPI average pain rating.

Safety:

Frequency of TEAEs, discontinuations due to AEs, and SAEs

Discontinuation rates

Change from baseline to endpoint in laboratory values

Change from baseline to endpoint in vital signs values and weight

Frequency of treatment-emergent abnormal laboratory values

Frequency of treatment-emergent abnormal vital signs values and weight

Frequency of suicide-related outcomes using C-SSRS

Statistical Evaluation Methods:

With 211 patients per treatment group, this study has approximately 85% power to detect a difference between duloxetine and placebo of 0.6 points in the mean change from baseline to endpoint in the BPI average pain rating, assuming a common standard deviation of 2.0. The sample size was determined using a 2-sided 2-sample t-test with α=0.05, assuming a discontinuation rate of 5% (dropout without post-treatment BPI rating). All the parameters used in the sample size calculation were based on the baseline-observation-carried-forward (BOCF) analysis of combined data from 2 OA knee pain studies for duloxetine (Study F1J-MC-HMEP and Study F1J-MC-HMFG).

All analyses were conducted on an intent-to-treat basis. Treatment and interaction effects were evaluated based on a 2-sided significance level of 0.05. No adjustments for multiple comparisons were made. Unless otherwise specified, when a total score was calculated from individual items, it was considered missing if any of the individual items were missing; when an average score was computed from individual items, it was calculated from non-missing values.

A BOCF analysis was used to analyze the primary efficacy variable (change from baseline in BPI average pain rating). An analysis of covariance (ANCOVA) model with terms for treatment, investigator, and continuous covariate of baseline BPI average rating was used to test treatment differences. Change from baseline in the primary efficacy variable was also analyzed by an ANCOVA model using a last-observation-carried-forward (LOCF) approach and a restricted maximum likelihood-based, mixed-effects repeated measures (MMRM) approach. Type III sum of squares for least-squares means (LSMeans) was used for statistical comparisons using ANCOVA models when no interaction term is involved. Type II sum of squares was used for the LSMeans when an interaction term was included.

Analyses of categorical safety variables (AEs, treatment-emergent changes in vital signs, and labs) were conducted using Fisher's exact test. Continuous safety data were analyzed using an ANOVA model.

The treatment differences between duloxetine 60 mg QD and placebo were originally planned to be tested. However, the study drug labeling error caused a cross-over in treatment administered between weeks 2 through 13 of the acute therapy phase. As a result, the treatment differences of the 2 resulting groups (relabeled as PLA_DLX60QD [pla-duloxetine] and DLX30_PLA [dlx-placebo]) were tested instead for the acute therapy phase.

Summary:

As previously described, the incorrect labeling, and resultant incorrect administration of study drug to all randomized patients in the 2 treatment groups, compromised the integrity of the entire study and rendered the planned comparisons between treatment groups and any resulting conclusions invalid.

For the primary efficacy endpoint, using BOCF analysis, a numerically greater pain reduction (improvement) was observed in the pla-duloxetine treatment group compared with the dlx-placebo treatment group, but the difference was not statistically significant (p=.105). When the primary outcome measure was analyzed using both the LOCF and MMRM approaches, the differences between the 2 treatment groups were statistically significantly different. Greater pain reduction (improvement) was observed for the pla-duloxetine group compared with the dlx-placebo group at endpoint (LOCF; p<.001) and at each visit (MMRM; p<.001).

A total of 424 patients were randomized to either pla-duloxetine (217) or dlx-placebo (207), of which 213 pla-duloxetine treated patients and 203 dlx-placebo treated patients received at least 1 dose of study drug.

No deaths occurred during the study. Four patients (1/217 [0.5%] pla-duloxetine and 3/207 [1.4%] dlx-placebo) reported 1 SAE each during the acute therapy phase. During Study Period III, 1 pla-duloxetine patient, who was switched to placebo, reported 1 SAE.

Of the 424 randomized patients, 333 (78.5%) completed the acute therapy phase while 91 patients (21.5%; 55 pla-duloxetine and 36 dlx-placebo) discontinued due to any reason. There was no statistically significant difference between treatment groups for frequency of completers (p=.058) or frequency of patients who discontinued due to any reason (p=.058) for the acute therapy phase. Statistically significantly more pla-duloxetine treated patients (16.1%) reported AEs as the reason for discontinuation, compared with dlx-placebo patients (7.2%; p=.006), and nausea was the only AE term that was reported significantly more frequently, as a reason for discontinuation, in the pla-duloxetine treatment group.

A total of 57.1% of study patients reported 1 or more TEAEs in Study Period II. Significantly more patients in the pla-duloxetine treatment group than in the dlx-placebo treatment group reported 1 or more TEAEs (64.5% versus 49.3%; p=.002). Statistically significantly more patients in the pla-duloxetine treatment group reported the following TEAEs than patients in the dlx-placebo treatment group: nausea, decreased appetite, fatigue, and hyperhidrosis. Most treatment-emergent adverse events (222/242; 92%) were mild or moderate in severity.

Using the C-SSRS, 1 event of suicidal ideation was reported in a dlx-placebo treated patient during the acute therapy phase.

Two pla-duloxetine-treated patients met the prespecified hepatic algorithm criteria (that is, patients with a normal baseline ALT and a treatment-emergent ALT ≥3 times the upper limit of normal at a postbaseline time point); neither patient had a concurrent elevation of bilirubin and both had final ALT (Visit 301) values of ≤75 units/L.

A significant difference was observed for fasting glucose, with the pla-duloxetine group showing a greater mean increase than the dlx-placebo group (p=.018). There were no statistically significant differences in glycosylated hemoglobin (A1C) changes between the treatment groups. Approximately 6% patients experienced an increase in fasting glucose levels of 1.5 mmol/L or more, with a similar distribution among patients in the pla-duloxetine and the dlx-placebo groups. A total of 13% of randomized patients reported diabetes mellitus as a pre-existing condition, with an equal incidence in each treatment group (13%).

Other significant differences between treatment groups were observed with GGT, alkaline phosphatase, chloride, and uric acid. These laboratory findings were generally consistent with laboratory findings in previous duloxetine studies, and given the overall incidence and magnitude of change, were considered not clinically relevant.

During the acute therapy phase, a decrease in diastolic blood pressure was observed in the pla-duloxetine group and an increase was observed in the dlx-placebo group, leading to a statistically significant difference in mean change from baseline between treatment groups (p=.036). There was a decrease in weight in the pla-duloxetine group and an increase in the dlx-placebo group, with a statistically significant difference in mean change from baseline between groups (p=.001). Also during the acute therapy phase, the dlx-placebo treatment group had a significantly higher incidence of patients (4.9%) with sustained elevation in blood pressure compared with the pla-duloxetine group (0.9%; p=.019).

The overall safety and tolerability profile observed in patients receiving pla-duloxetine during this study was generally consistent with the known safety and tolerability profile of duloxetine.

Conclusions:
The magnitude of average pain improvement, as assessed by the primary outcome measure, for the pla-duloxetine treatment group was similar to that reported in previous duloxetine pain studies. The extent to which duration of treatment and discontinuation rates were impacted by study drug mislabeling and the cross-over administration of study drug is difficult to assess.

Overall, despite the lack of up-titration and taper of doses, duloxetine 60 mg QD was fairly well tolerated.